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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,913	12/31/2001	Ulf Landegren	LAND DIV	5983

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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HC

Office Action Summary	Application No.	Applicant(s)	
	10/029,913	LANDEGREN, ULF	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/171935.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.S

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 6/7/2005 have been entered.

This action is written in response to applicant's correspondence submitted 6/7/2005. claims 1-32 have been canceled, and claims 33-42 have been added. Claims 33-42 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims while new grounds of rejection also exist.

Claim Objections

Claims 33-42 are objected to since in claim 33 step b) there exist the following informalities: It is not clear what applicant means to be claiming with the recitation of "target nucleic acid sequence conditions". It is assumed that applicant inadvertently inserted "conditions" at the end of the phrase since it had been present in previous claim versions. Appropriate correction is required.

Claim 33 is also objected to considering its recitation of "a method wherein a target nucleic acid sequence comprising" is lacking any sort of completion to its wherein clause.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It should be noted that the art rejections have been made in light of the claim objections above and in light of the particular interpretations of limitations recited in the claims(see below rejection).

1. Claims 33, 36, 37, and 40-41 are rejected under 35 U.S.C. 102(b) as being unpatentable over Nilsson et al.(Science, Vol. 265, pages 2085-2088 September 30, 1994).

With regard to claim 33, a cleavable, detectable function is broadly interpreted to include anything that is removable and detectable. For example, a nucleotide that is exonuclease-treated and detected(e.g. via hybridization or fluorescence) is interpreted as meeting this claim limitation. Nilsson et al. teaches a method of detecting a target nucleic acid sequence in a sample by contacting the sample with a detectable probe to hybridize the probe to the target sequence, and detecting the hybridized probe, said probe has two free nucleic acid end parts which are at least partially complementary to and capable of hybridizing to two at least substantially neighboring regions of the target sequence (Figure 4 description), comprising the following steps:

a) immobilizing an oligonucleotide probe to a solid support via a solid phase anchor(the solid support being a nylon membrane). In the absence of any explicit definition in the specification the solid phase anchor is being interpreted as being the immobilized plasmid clones see page 2086 right side that when bound to by the oligonucleotide probes, anchors the oligonucleotide probes to the solid phase. Furthermore said immobilized probe comprises at least one 3'-end sequence (eg. see figure 3 description "CTT"), an intermediate sequence comprising a solid phase anchor (taught in the sequence comprised by any nucleotide between the 3' and 5' most nucleotides which hybridizes to the solid phase anchor[immobilized target DNA]), and at least one 5' end the probe comprising three regions including a detectable function("as the probes were labeled by the addition of a radioactive phosphate group at the 5' terminus(Pg. 2086 upper left), cleavable site(multiple such sites exist along the length of the probe's 5'end that separate following a denaturing wash) that is between the detectable function sequence and the solid phase anchor, eg, the hydrogen bonds holding the two sequences together), and the solid phase anchor(clone DNA). It should be noted that applicant's use of "comprising" in their claim broadens the way in which their probe's structure is interpreted.

b) hybridizing the probe ends to the target sequence under hybridization conditions (Figure 4 description);

c) covalently connecting the ends of the hybridized probe with each other to form a circularized structure;(Figure 4 description)

d) cleaving the cleavable function (e.g. washing under denaturing conditions in this case) (Figure 4), characterized in that the probe is provided with a cleavable or dissociable detectable function (Figure 4 description), and the method comprising the further steps of:

e) separating detectable functions no longer linked to the solid phase (Figure 4 description);

f) detecting the presence and, if desired, location of the remaining probe as indicative of the presence of the target nucleic acid sequence (Figure 4 description).

With regard to claims 36 and 37, Nilsson et al. teaches that the detectable function is dissociable by being provided either on a further circularizable probe or on a target-specific probe (Figure 4 description) such as the one described for an alphoid repeat-motif present on chromosome 12.

With regard to claim 40, Nilsson et al. further teaches the performance covalent connection of the probe ends by enzymatic or chemical ligation (Figure 4 description).

With regard to claim 41, Nilsson et al. teaches the DNA or RNA as target molecule (Figure 4 description).

Response to Arguments

Applicant's arguments filed 6/7/2005 have been fully considered but they are not persuasive. Applicant first asserts that their newly found limitation in claim 33 should be noted by the examiner which recites a step of immobilizing a probe. The probe comprising at least one 3' end sequence, an intermediate sequence comprising a solid phase anchor, and at least one 5' end sequence wherein the 3'end sequence or 5' end sequence further comprises at least one detectable function and a cleavable site between the detectable function and the solid phase. It is maintained that this broad recitation in the claim does not limit applicant's invention to that which is depicted in figure 1 of their current drawings. As the claims are currently written it is maintained by the office that the Nilsson et al. reference still anticipates their newly recited

limitation as can be seen in the far right column of page 2086 in the reference's use of immobilized clone DNA, its attachment to a solid support, each probe containing three regions, and the step of using a denaturing wash to interrupt hybridization between DNA molecules at cleavable sites. Applicant is reminded that only the claims define the invention and that furthermore, that limitations in applicant's arguments, specification etc cannot be read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, without a requirement for the methods particular, constituent steps mentioned on pages 7 and 8 for example, the art will be applied as broadly as the claims are written. The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*,415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). As was stated previously in response to applicant's arguments, additional explanations for maintaining the rejection exists for example, when a nucleotide that is exonuclease-treated or cleaved and detected in any way(e.g. run on a gel) this is interpreted as meeting this claim limitation. Further, as can be seen on page 4 of the Official Action, "cleaving the cleavable function" is interpreted broadly to be taught by a step of washing under denaturing conditions(see Figure 4 description) which is interpreted as teaching the broadly claimed and undefined, "cleaving and cleavable function". In response to applicant's second argument regarding their interpretation that " the probes do not contain a solid phase anchor", in the absence of any definition in the specification or claims, the limitation is met by Nilsson's teaching of the probes bound to a slide in the description of Figure 4 but also DNA is immobilized on a nylon membrane in another

example.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 34, 35 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al.(Science, Vol. 265, pages 2085-2088 September 30, 1994) in further view of Urdea et al.(US Patent 5,124,246).

With regard to claim 33, a cleavable, detectable function is broadly interpreted to include anything that is removable and detectable. For example, a nucleotide that is exonuclease-treated and detected(e.g. via hybridization or fluorescence) is interpreted as meeting this claim limitation. Nilsson et al. teaches a method of detecting a target nucleic acid sequence in a sample by contacting the sample with a detectable probe to hybridize the probe to the target sequence, and detecting the hybridized probe, said probe has two free nucleic acid end parts which are at least partially complementary to and capable of hybridizing to two at least substantially neighboring regions of the target sequence (Figure 4 description), comprising the following steps:

a) immobilizing an oligonucleotide probe to a solid support via a solid phase anchor(the solid support being a nylon membrane and the solid phase anchor being the immobilized plasmid clones see page 2086 right side) the probe comprising three regions including a detectable function, cleavable site(between the detectable function sequence and the solid phase anchor, eg, the hydrogen bonds holding the two sequences together), and the solid phase anchor(clones).

b) hybridizing the probe ends to the target sequence under hybridization conditions (Figure 4 description);

c) covalently connecting the ends of the hybridized probe with each other to form a circularized structure;(Figure 4 description)

d) cleaving the cleavable function (e.g. washing under denaturing conditions in this case) (Figure 4), characterized in that the probe is provided with a cleavable or dissociable detectable function (Figure 4 description), and the method comprising the further steps of:

e) separating detectable functions no longer linked to the solid phase (Figure 4 description);

f) detecting the presence and, if desired, location of the remaining probe as indicative of the presence of the target nucleic acid sequence (Figure 4 description).

With regard to claims 36 and 37, Nilsson et al. teaches that the detectable function is dissociable by being provided either on a further circularizable probe or on a target-specific probe (Figure 4 description).

With regard to claim 40, Nilsson et al. further teaches the performance covalent connection of the probe ends by enzymatic or chemical ligation (Figure 4 description).

With regard to claim 41, Nilsson et al. teaches the DNA or RNA as target molecule (Figure 4 description).

Nilsson et al. also do not teach the method with branched or bifurcated probes with regards to claims 34 and 35.

However, Urdea et al. teaches the above method wherein one or both of the probe ends have at least two branches, and a detectable function is provided on each of the branches on one end part of said probe, the detectable functions being different and distinguishable from each other and a circularizable probe comprising two free cleavable or detectable nucleic acid end parts which are linear, branched or bifurcated and are capable of hybridizing to two at least substantially neighboring regions of a target sequence (abstract, examples 1, 2 and 3). Specifically, in Column 17 lines 45-55, Urdea teaches that various techniques may be employed for detecting the presence of the label.

Nilsson et al. also do not teach the immobilization via biotin to a streptavidin-coated solid phase with regard to claim 42.

However Urdea et al teach in Column 16 lines 29-31 that examples of such pairs of oligonucleotides attached to solid phase are "biotin/avidin".

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the branched or bifurcated probes of Urdea et al. and the ligand receptor binding pair of "biotin/avidin" in the method of Nilsson et al. since Urdea et al state, "suitable cleavable linker molecules may be incorporated into the multimers at predetermined sites for the purpose of analyzing the structure of the multimer or as a means for releasing predetermined segments (such as the portion of the multimer that binds to the

oligonucleotide) (Column 12, lines 49-55)99. Moreover, Urdea et al. states "The multimers may be used in essentially any of the known nucleic acid hybridization formats, such as those in which the analyte is bound directly to a solid phase or a sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase (Column 13, lines 56-61)". An ordinary practitioner would have been motivated to combine and substitute the branched or bifurcated probes of Urdea et al. into the method of Nilsson et al. in order to achieve the express advantages, as noted by Urdea et al., of improving the sensitivity of nucleic acid based assay by applying multimers, which may be used in essentially any of the known nucleic acid hybridization formats, such as those in which the analyte is bound directly to a solid phase or sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase.

Response to Arguments

Applicant's arguments filed 6/7/2005 have been fully considered but they are not persuasive. No new arguments are presented in response to this rejection that hasn't already been addressed above in response to the 102(b) rejection, applicant should reference the above response.

3. Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al.(Science, Vol. 265, pages 2085-2088 September 30, 1994) in further view of Birkenmeyer et al.(US Patent 5,427,930).

While the teachings of Nilsson et al. are summarized above, the reference does not teach the interspace between probe ends which is filled by an extension reaction prior to covalently interconnecting the probe ends.

However, Birkenmeyer et al. teaches the interspace between probe ends which is filled by an extension reaction prior to covalently inter-connecting the probe ends (abstract and example 1). It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute gap filling ligase chain reaction in the method of Nilsson et al. since Birkenmeyer et al. states "it is therefore a primary object of the present invention to improve the sensitivity of nucleic acid based assay by decreasing the occurrence of target independent ligation which causes falsely positive background signal. This object is met in the present invention by modifying at least one probe end so that when hybridized with its complementary probe, the resulting duplex is not "blunt-ended" (i.e. ligatable) with respect to the partner complementary probe duplexes. After hybridization to the target, the modified ends are "corrected" in a target dependent fashion to render the adjacent probes ligatable. Several features of the probes and the associated target sequences taught in this application makes this task particularly elegant (column 2, lines 28-42)". An ordinary practitioner would have been motivated to combine gap filling ligase chain reaction into the method of Nilsson et al. in order to achieve the express advantages, as noted by Birkenmeyer et al., of improving the sensitivity of nucleic acid based assay by decreasing the occurrence of target independent ligation.

Response to Arguments

Applicant's arguments filed 6/7/2005 have been fully considered but they are not persuasive. Applicant's argue that Birkenmeyer et al. "teach away from the claimed invention"

since applicant's invention "are optimally designed to hybridize to a target molecule to leave a small gap between adjacent probe ends". However, as can be read above, applicant cannot read limitations of the specification(e.g. page 4, lines 29-31) into their claims, and this limitation is not presently recited in applicants claims. As a result the presently cited Birkenmeyer et al. reference is deemed appropriate in light of the presently written claim limitations.

Claim Rejections - 35 USC § 112- New Matter

4. Claims 33-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "an intermediate sequence comprising a solid phase anchor" in claim 33 appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the basis for the amendments as cited by applicant as page 6, line 38 to page 7 line 1, page 4 line 36, page 9 lines 30-32 of the specification lead the examiner to any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 33-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 33-42 are indefinite over the recitation of "an intermediate sequence" in claim 33 step a). It is not clear if what it means for the sequence to be intermediate, i.e. is that the sequence is between the 3' and 5' ends of the probe and that the sequence alone functions as an anchor or instead is the intermediate sequence a nucleotide sequence that is bound to a solid phase anchor, not directly located between the two ends of the probe on the DNA strand. Furthermore, it is not clear what intermediate means concerning the 3' and 5' ends of the probe, is a single nucleotide 5'of the 3' enough to be intermediate to the two ends? It is further not clear if the solid phase anchor is a part of the intermediate sequence, is the intermediate sequence or merely just attaches to the intermediate sequence as stated above. The actual definition of intermediate is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes an intermediate sequence comprising a solid phase anchor.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris

8/30/2005

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